

## CLAIMS

1. A computer-implemented method for statistical analysis of QT interval as a function of changes in the RR interval before and after administration of a dose of a compound, the method comprising the steps of:

5        comparing a pre-dose curve of QT interval versus RR interval to a post-dose curve of QT interval versus RR interval;

         determining the incidence of points of the post-dose curve that exceed an upper single-point prediction limit of the pre-dose curve to determine the degree of heterogeneity of ventricular repolarization; and

10        determine the magnitude that these points exceed the pre-dose QT curve and provide a quantitative assessment of treatment-induced changes in the QT-RR relationship.

2. A computer-implemented method as recited in claim 1, wherein the pre-dose curve to post-dose curve comparison step comprises the substeps of:

15        using an equation to fit each QT measurement to a preceding, or set of preceding, RR intervals and provide the pre-dose curve and post-dose curves; and

         comparing the pre-dose and post-dose curves to determine if and at what point the post-dose curve becomes significantly higher than the pre-dose curve.

20        3. A computer-implemented method as recited in claim 1, wherein the compound is administered to a human.

4. A computer-implemented method as recited in claim 1, wherein the determining step comprises the substeps of:

         pooling the confidence limits for the pre-dose and post-dose curves to provide an estimate of the standard error of the difference between the two curves;

25        using the single-point upper 95% prediction limit for the pre-dose curve to determine whether a QT point on the post-dose curve is significantly prolonged;

         conducting a repeated measures test for significance to evaluate an overall effect of the treatment over all of the time periods; and

30        conducting individual significance tests of the proportion of prolonged outliers to determine if the treatment response is significantly higher than the pre-dose curve.

5. A computer-implemented method as recited in claim 1, wherein the step of comparing the points of the post-dose data that exceed the upper 95% single-point prediction limit to the pre-dose curve comprises the substeps of:

comparing outliers to the pre-dose curve to estimate how far above the pre-dose curve they are prolonged;

subtracting the post-dose outliers from the pre-dose curve to provide corrected  $\Delta$ QT values;

5 comparing the corrected  $\Delta$ QT values within treatment groups, post-dose to pre-dose, and across treatments;

conducting an overall test to compare the mean  $\Delta$ QT of each group; and

conducting a one-sided significance test on the  $\Delta$ QT values.

6. A computer readable medium that stores instructions executable by one or  
10 more processors to perform statistical analysis of QT interval as a function of changes in the RR interval before and after administration of a dose of a compound, the computer-readable medium comprising:

instructions for comparing a pre-dose curve of QT interval versus RR interval to a post-dose curve of QT interval versus RR interval;

15 instructions for determining the incidence of points of the post-dose curve that exceed an upper 95% single-point prediction limit to determine the degree of heterogeneity of ventricular repolarization; and

instructions for comparing the points of the post-dose data that exceed the upper 95% single-point prediction limit to the pre-dose curve to determine the  
20 magnitude of these points and provide a quantitative assessment of treatment-induced changes in the QT-RR relationship.

7. A computer readable medium as recited in claim 6, wherein the instructions for comparing the pre-dose curve to post-dose curve comprise:

instructions for using an equation to fit each QT measurement to a preceding  
25 RR interval and provide the pre-dose curve and post-dose curves; and

instructions for comparing the pre-dose and post-dose curves to determine if and at what point the post-dose curve becomes significantly higher than the pre-dose curve.

8. A computer readable medium as recited in claim 6, wherein the compound is  
30 administered to a human.

9. A computer readable medium as recited in claim 6, wherein the instructions for determining the incidence of points of the post-dose data that exceed the upper 95% single-point prediction limit comprise:

instructions for pooling the confidence limits for the pre-dose and post-dose curves to provide an estimate of the standard error of the difference between the two curves;

5 instructions for using the upper 95% single-point prediction limit for the pre-dose curve to determine whether a QT point on the post-dose curve is significantly prolonged;

instructions for conducting a repeated measures test for significance to evaluate an overall effect of the treatment; and

10 instructions for conducting individual significance tests of the proportion of prolonged outliers to determine if treatment is significantly higher than the pre-dose curve.

10. A computer readable medium as recited in claim 6, wherein the instructions for comparing the points of the post-dose data that exceed the upper 95% single-point prediction limit to the pre-dose curve comprise:

15 instructions for comparing outliers to the pre-dose curve to estimate how far above the pre-dose curve they are prolonged;

instructions for subtracting the data of the post-dose curve from the data of the pre-dose curve to provide corrected  $\Delta$ QT values;

20 instructions for comparing the corrected  $\Delta$ QT values between treatments; and instructions for conducting an overall test to compare the magnitudes of each treatment  $\Delta$ QT.

11. A system for statistical analysis of QT interval as a function of changes in the RR interval before and after administration of a dose of a compound, the system comprising:

25 a memory configured to store instructions; and a processor configured to execute instructions for:

comparing a pre-dose curve of QT interval versus RR interval to a post-dose curve of QT interval versus RR interval,

30 determining the incidence of points of the post-dose data that exceed an upper 95% single-point prediction limit to determine the degree of heterogeneity of ventricular repolarization, and

comparing the points of the post-dose data that exceed the upper 95% single-point prediction limit of the pre-dose curve to determine the

magnitude of these points and provide a quantitative assessment of treatment-induced changes in the QT-RR relationship.

12. A system as recited in claim 11, wherein the instructions for comparing the pre-dose curve to post-dose curve comprise:

5 instructions for using an equation to fit each QT measurement data to the corresponding preceding RR interval measurement data and provide the pre-dose curve and post-dose curves; and

instructions for comparing the pre-dose and post-dose curves to determine if and at what point the post-dose curve becomes significantly higher than the pre-dose  
10 curve.

13. A system as recited in claim 11, wherein the compound is administered to a human.

14. A system as recited in claim 11, wherein the instructions for determining the incidence of points of the post-dose curve that exceed the upper 95% single-point  
15 prediction limit comprise:

instructions for pooling the confidence limits for the pre-dose and post-dose curves to provide an estimate of the standard error of the difference between the two curves;

instructions for using the upper 95% single-point prediction limit for the pre-  
20 dose curve to determine whether a QT point on the post-dose curve is significantly prolonged;

instructions for conducting a repeated measures test for significance to evaluate an overall effect of the compound over all of the time periods; and

instructions for conducting individual significance tests of the proportion of  
25 prolonged outliers to determine if any one dose of the treatment is significantly higher than the pre-dose curve.

15. A system as recited in claim 11, wherein the instructions for comparing the points of the post-dose curve that exceed the upper 95% single-point prediction limit to the pre-dose curve comprise:

30 instructions for comparing outliers to the pre-dose curve to estimate how far above the pre-dose curve they are prolonged;

instructions for subtracting the post-dose data from the pre-dose curve to provide corrected QT values ( $\Delta$ QT);

